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PII: S0040-4039(13)02005-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.11.058
Reference: TETL 43853

To appear in: *Tetrahedron Letters*

Received Date: 29 October 2013
Revised Date: 14 November 2013
Accepted Date: 16 November 2013

Please cite this article as: Walz, A.J., Hsu, F-L., Synthesis of 4-anilinopiperidine methyl esters, intermediates in the production of carfentanil, sufentanil, and remifentanil, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.11.058

Synthesis of 4-anilinopiperidine methyl esters, intermediates in the production of carfentanil, sufentanil, and remifentanil

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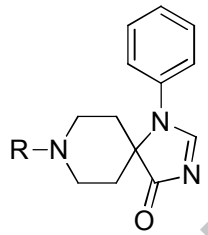
Abstract:



R = Bn or CH_2CH_2Ph

Two spirodiaza intermediates have been made and employed in the synthesis of 4-anilinopiperidine methyl esters. These intermediates can be utilized in the production of commercial synthetic analgesics carfentanil, sufentanil, and remifentanil.

Keywords:

Anilinopiperidine methyl esters

Cyclization

Sufentanil

Carfentanil

Remifentanil

N,N-Dimethylformamide dimethyl acetal

4-Anilidopiperidines are potent synthetic opioids employed as analgesics worldwide.[1] Janssen and coworkers have produced many potent and clinically useful

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compounds.[2-5] A potent, short acting analog was later developed by Feldman et al.[6](**Figure 1**) These analgesics have been prescribed as potent sedatives for large animals (carfentanil) and humans (sufentanil and remifentanil).

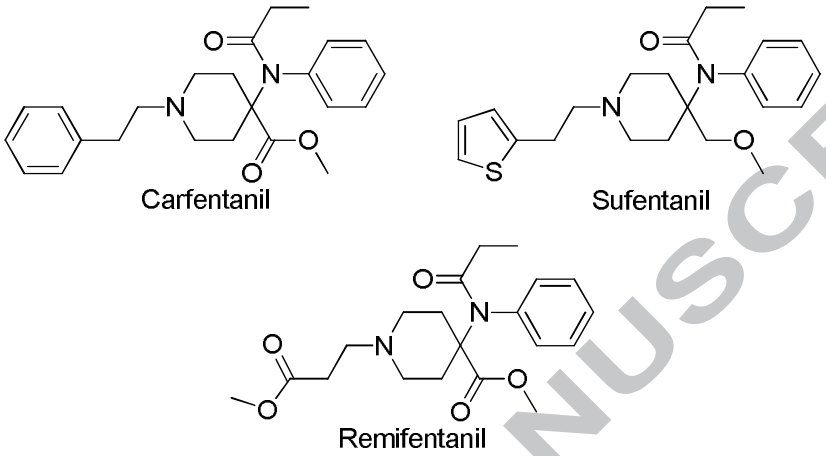
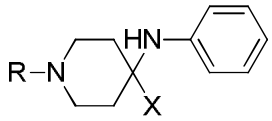


Figure I: Structures of some synthetic opioids.

The synthesis of these compounds, as developed by Janssen, incorporated the stepwise conversion of the C-4 nitrile of 1-benzyl-4-(phenylamino)piperidine-4-carbonitrile to a methyl ester.(**Figure 2**)



R = Bn or CH_2CH_2Ph
X = CN to $CONH_2$ to CO_2H to CO_2Me

Figure 2: Nitrile to methyl ester chemistry.

The synthesis utilized a sulfuric acid-mediated nitrile conversion to an amide followed by basic hydrolysis to a carboxylic acid. The acid was then alkylated to the methyl ester using methyl iodide in DMSO. This methodology has been applied to both the N1-benzyl and N1-(2-phenylethyl) substituted piperidines.

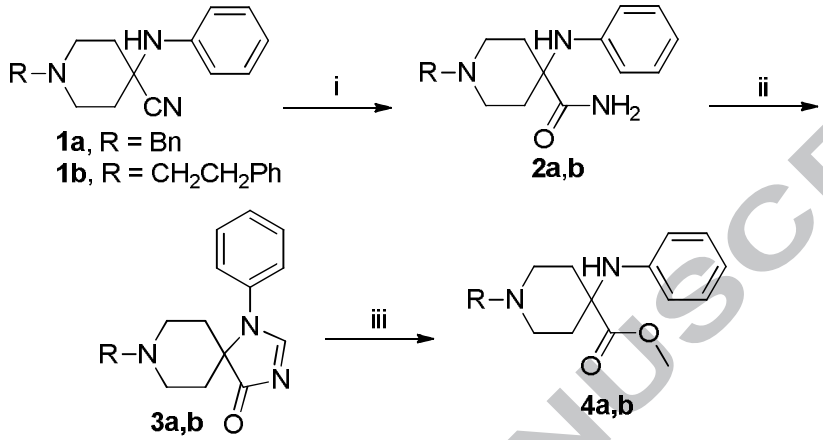
The analgesic potency of the synthetic opioids generated interest in improving the original chemistry used to produce them. With the N1-benzyl substituted piperidines, work was done on both the nitrile and amide functional group transformations. The nitrile to amide conversion was accomplished using DMSO/hydrogen peroxide.[7] The conversion of the nitrile to a hydantoin as a precursor to the carboxylic acid was accomplished.[8] The C-4 carboxylic acid was formed from the amide employing acidic conditions.[9] Kiessling and McClure applied trimethyloxonium tetrafluoroborate to the amide to form an imidate which was then converted to the methyl ester.[10] A direct conversion of the amide to the methyl ester utilizing methanolic p-toluenesulfonic acid was reported.[11]

Utilization of N1-(2-phenylethyl) substituted piperidines in **Figure 2** results in a more direct synthesis of carfentanil. The Janssen reaction sequence was employed yet was limited by a 14% isolated yield for the amide formation.[3,12] Reiff and Sollman developed an alternative amide synthesis.[13] Formylation of the aminonitrile was followed by imidate formation in methanolic HCl with concomitant formyl group cleavage. The imidate was hydrolyzed to the amide in a 49% isolated yield for the three step process. The DMSO/peroxide mediated amide formation has been successfully applied in an 84% yield.[14] The reaction reported was done at less than 100 milligram scale with no spectral data reported. A similar basic peroxide reaction was reported with a 44% yield of the amide on a multigram scale.[15] As with the benzyl series, the amide was converted to the methyl ester via a carboxyl group.

This letter reports improvements on the synthesis of 4-anilinopiperidine methyl esters **4a**,**b** as seen in **Scheme 1**. The chemistry utilizes 4,4-(2-phenyl-2,4-diaza-4-

oxo-cyclopentane)piperidines **3a**,**b**. The literature references compound **3a** but not as an intermediate in the synthesis of 4-anilinopiperidine methyl esters.[16,17,18]

Scheme 1



Reagents: i) CF_3COOH, H_2SO_4. ii) N,N-dimethylformamide dimethyl acetal, CH_3OH. iii) H_2SO_4, CH_3OH.

Hydrolysis of nitriles to amides utilizing trifluoroacetic acid and sulfuric acid has also been reported.[19] This methodology was applied to compounds **1a**,**b** to provide amides **2a**,**b** which were purified by recrystallization from toluene. It should be noted that the use of sodium hydroxide to neutralize the acid and hydrolyze the presumed intermediate imidate was necessary for consistently good yields of **2b** while ammonium hydroxide could be used for the work up of **2a**.

N,N-Dimethylformamide dimethyl acetal has been shown to convert amides to methyl esters.[20] When reacted with compounds **2a**,**b** in methanol at 65°C, cyclization to the phenyl-2,4-diaza-4-oxo-cyclopentane ring was overwhelmingly favored over methyl ester formation. After evaporation of the volatiles, crude **3a**,**b** were both recrystallized from toluene. In our hands, overnight refluxing of **2a** or **2b** in trimethyl orthoformate produced negligible cyclization products.

The conversion of the spirodiaza intermediate **3a** to methyl ester **4a** was achieved in methanol with 1.2 to 1.4 molar equivalents of sulfuric acid at 95°C in a pressure bottle. The same methanolysis of **3b** was accomplished but was particularly sensitive to the amount of acid utilized with 1.2 equivalents of sulfuric acid being optimal. Increasing the amount of sulfuric acid led to extended reaction times and an increase in unwanted side reactions. It should be noted that following an aqueous work up, the organic extracts containing compound **4b** were filtered through Celite on top of a 10 g layer of activated basic Brockmann I alumina to decolorize the solution. Both **4a**,**b** were purified by conversion to their oxalate salts in ethanol. A two step/one pot conversion of **2a** to **4a** was attempted but generated a by-product which could not be separated by recrystallization.

The three-step transformation of nitriles **1a**,**b** to the methyl esters **4a**,**b** has been improved over the existing literature methods. The reactions were operationally simple and no chromatographic purifications were required. No reactions were run for greater than 16 h and none exceeded a reaction temperature of 95°C. Nitrile hydrolysis was accomplished in good yields for both the N1-benzyl and N1-(2-phenylethyl) piperidines using trifluoroacetic acid and sulfuric acid. While the conversion of **1a** to **2a** did not distinguish itself from the existing methodology, the 78% isolated yield of **2b** did demonstrate a notable improvement. The N,N-dimethylformamide dimethyl acetal cyclization reaction clearly improved this transformation in terms of reaction conditions and length compared with literature precedents. The same cyclization of **2a** to **3a** had been previously accomplished by an overnight amine formylation followed by a seven day reflux in triethyl orthoformate.[15] Janssen accomplished a similar cyclization with

formamide and an inorganic acid at 170°C for 12 h.[16,17] Good yields were obtained with either N1-benzyl or N1-(2-phenethyl) substituted intermediates. Finally, the methanolysis of the 4,4-(2-phenyl-2,4-diaza-4-oxo-cyclopentane)piperidines **3a**,**b** were cleanly accomplished to efficiently provide the 4-anilinopiperidine methyl esters.

Supplementary Material

Experimental procedures are reported with copies of the NMR and mass spectra.

Acknowledgements

The authors would like to thank Dr. Sari Paikoff at the Defense Threat Reduction Agency-Joint Science and Technology Office (DTRA-JSTO) for funding this work under contract (CBCALL12-TAS-2-0130).

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